

## Age at Menopause: Do Chemical Exposures Play a Role?

Charles W. Schmidt

With its associated hot flashes, mood swings, and insomnia, menopause can be a challenging period in a woman's life. But as much as it marks the end of her childbearing years, menopause—and more specifically the age at which it occurs—can also reflect on a woman's overall health. An older age at menopause typically reflects good health overall, whereas early menopause—generally defined as occurring before age 40—can reflect poorer health and a greater likelihood of premature mortality.<sup>1</sup>

Now, experts are taking a closer look at how environmental exposures may influence age at menopause and whether exposure-induced changes in menopausal timing put women at greater risk of associated health problems. These are early days in the field, but recent research suggesting a link between potential endocrine-disrupting compounds (EDCs) and early menopause<sup>2,3</sup> has raised concerns over how exposures might accelerate hormonal processes involved in female aging.

“We know that going through menopause early increases the risk of osteoporosis, heart disease, and other disorders,” says Natalia Grindler, a reproductive and endocrinology fellow at the University of Colorado's Advanced Reproductive Medicine Division. “So the long-term health implications of early menopause are considerable.”

There is still much to be learned about the toxicology underlying changes in age at menopause, and isolating chemical effects from the other varied influences that govern when a woman's reproductive years come to an end is challenging. Nevertheless, this area of study provides a new window on population-level effects from chemical exposures that could have wide-ranging consequences.

### Mechanisms of Menopause

The fact that exogenous exposures can shorten the time to menopause first became evident during the 1970s, when research began linking early menopause with exposure to tobacco smoke.<sup>4,5</sup> Scientists have since reported associations with other environmental chemicals, including dioxins, polychlorinated biphenyls (PCBs), and phthalates.<sup>1,3,6</sup> To grasp how chemicals might hasten menopause, however, one first needs to understand the underlying hormonal system affected by exposure.

Healthy females are born with two ovaries, each filled with millions of immature eggs (oocytes) surrounded by specialized granulosa cells. By the time a girl reaches puberty, this number will have dwindled to approximately 400,000, of which just 400 or so eggs will become available for fertilization during the course of her life.

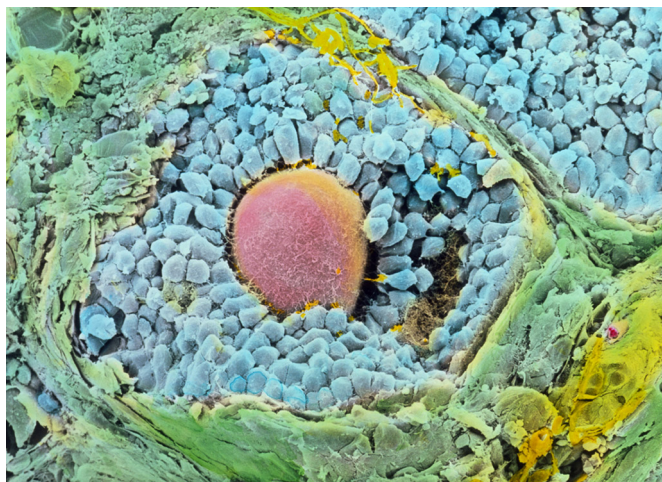
The menstrual cycle starts with the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. GnRH triggers the anterior pituitary gland to secrete follicle-stimulating hormone (FSH), which in turn initiates development of the follicle containing the oocyte, leading toward ovulation: the oocyte begins to mature, and the granulosa cells start secreting estrogen. When estrogen levels are sufficiently high, they cause the anterior pituitary to secrete luteinizing hormone (LH), which induces ovulation, or the release of the egg for fertilization.

The transition into natural menopause—as opposed to menopause caused by surgery (e.g., removal of the ovaries because of fibroids) or medication (e.g., chemotherapy)—is known as perimenopause. This transition typically begins in a woman's



With its associated hot flashes, mood swings, and insomnia, menopause can be a challenging period in a woman's life. But as much as it marks the end of her childbearing years, menopause—and more specifically the age at which it occurs—also reflects on a woman's overall health. © sylvlrobl/ShutterstockImage.

mid-40s,<sup>7,8</sup> when the functioning of the ovaries becomes inconsistent. “Perimenopausal women have irregular menstrual cycles, and it is not clearly understood if that has something to do with reduced function of the pituitary gland, or if it is because the ovarian follicles are not functioning adequately,” says Patricia Hoyer, a professor of physiology and of pharmacology and toxicology at the University of Arizona College of Medicine.



Healthy females are born with two ovaries, each filled with millions of immature eggs (oocytes) surrounded by specialized granulosa cells. In the menstrual cycle, gonadotropin-releasing hormone (GnRH) triggers the anterior pituitary gland to secrete follicle-stimulating hormone (FSH), which in turn initiates development of the follicle containing the oocyte, leading toward ovulation: the oocyte begins to mature, and the granulosa cells start secreting estrogen. When the estrogen level is sufficiently high, it causes the anterior pituitary to secrete luteinizing hormone (LH), which induces ovulation, or the release of the egg for fertilization. © Prof. P.M. Motta, G. Macchiarelli, S.A. Nottola/Science Source.

During perimenopause, declining estrogen output by the ovaries causes FSH and LH levels to remain elevated as the pituitary gland attempts to drive ovulation. Indeed, along with cessation of menstrual periods, menopause is marked by declines in estrogen and persistent elevations in FSH. According to Hoyer, erratic estrogen output likely accounts for the mood changes that characterize perimenopause; the biology driving hot flashes is more uncertain, although it may involve GnRH and estrogen.

### Variations on Normal

In 2013, Ellen Gold, a professor of public health sciences at the University of California, Davis, School of Medicine, reported 52.54 years as the median age at natural menopause among 3,302 women from five racial/ethnic groups living throughout the United States.<sup>9</sup> That figure came from her analyses of data collected by the Study of Women's Health Across the Nation (SWAN), which is a longitudinal multicenter investigation of female aging that launched in 1994.

Studies in other populations around the world have reported varying typical ages at natural menopause, at least in part because of differences in risk factors across the study populations examined. Gold also points out that because age at menopause is variable, outliers in the population unduly influence the average. "Many . . . papers have used the mean, i.e., the average, which will reflect the skewing of the distribution, usually to the younger ages," she explains. The median, she says, is a better statistical measure than the mean for nonnormal distributions such as menopausal age, and is therefore the more accurate representation of the typical age that applies to most women.

According to Gold, a woman's age at natural menopause depends on myriad factors, including genetics, body weight, physical activity, smoking, and contraceptive use. Gold says that women from the SWAN cohort who reported higher education levels, consistent employment, and good overall health tended to have a later age of menopause than women who did not. Earlier reports that menopausal age varies by race and ethnicity<sup>10,11,12</sup> were not supported after behavioral and health variables among women in the SWAN cohort were adequately controlled.<sup>9</sup>

Associations between early menopause and greater health problems may be related in part to declining estrogen levels.



Age at menopause is partly determined by genetics among other factors, including body weight, physical activity, smoking, and contraceptive use. In 2013, Ellen Gold reported 52.4 years as the median menopausal age among 3,302 women from five racial/ethnic groups living throughout the United States. © Monkey Business Images/Shutterstock.

Gold says that natural (endogenous) estrogen protects premenopausal women against cardiovascular disease and bone loss and fractures, which are both comparatively greater causes of morbidity and death in older women. In postmenopausal women, use of hormone replacement therapy—which utilizes synthetic versions of estrogen and progesterone—is protective against bone loss and fractures. However, it can also elevate a woman's risk for breast, endometrial, and ovarian cancers, and if it is used for more than a couple of years past the final menstrual period, it may also increase the risk of cardiovascular disease.

Numerous studies have associated a later age at natural menopause with lower risks of all-cause mortality, cardiovascular disease, and osteoporosis,<sup>13,14,15,16</sup> and there is evidence that an earlier age at menopause likewise heightens risks for these same outcomes.<sup>15,17,18,19</sup> For instance, a 2016 systematic review and meta-analysis of 32 studies found a 50% increased risk of heart disease among women who underwent menopause at 45 years of age or younger.<sup>20</sup> However, more research is needed to assess how lesser reductions in menopausal age could affect cardiac health and other disease risks.

### Assessing the Evidence

The exposure associated most consistently with earlier menopausal age is smoking. Studies show that women who smoke stop menstruating an average of 1–2 years earlier than comparable nonsmokers.<sup>1,21</sup> "While a one- to two-year reduction in age at menopause may not seem like much on the individual level, the potential public health impact is large, given the potential consequences for cardiovascular disease and other leading causes of mortality," Gold says.

Some evidence suggests that a woman's genetic makeup modifies this relationship, with preliminary evidence showing that heavy smokers who carried a certain variant of the *CYP3A4\*1B* gene were more likely to enter menopause within the study period than nonsmoking women who carried the same mutation.<sup>22</sup>

It has not been established whether the risk of early menopause is alleviated if a woman quits smoking. "My view is that former smokers may experience a risk of menopause that is earlier than women who never smoked and likely not as accelerated as active—especially heavy—smokers," says Samantha Butts, an associate professor of obstetrics and gynecology at the University



Older age at menopause reflects good health overall, whereas menopause at younger ages reflects poorer health and a greater likelihood of premature mortality. Going through menopause early also increases the risk of osteoporosis, heart disease, and other disorders. © Véronique Burger/Science Source.



of Pennsylvania. She adds that other factors (including genetic background, family history, and other medical comorbidities) interact with smoking history of any duration to influence menopausal timing.

Recently, investigators reported that secondhand smoke exposure also was associated with shorter time to menopause. A review of data from the Women's Health Initiative observational study, a prospective cohort of postmenopausal women from 40 centers across the United States estimated that non-smoking women exposed to the highest levels of secondhand smoke reached menopause an average of 13 months sooner than nonsmokers who were not exposed to secondhand smoke.<sup>22</sup>

Evidence shows that hydrocarbons in tobacco smoke induce early menopause by multiple pathways: by reducing the number of primordial and larger developing follicles, by inhibiting estrogen synthesis, and by enhancing the metabolism of estrogen in the liver.<sup>23,24</sup> Plausible mechanisms by which other environmental chemicals induce early menopause are somewhat more speculative.

Scientists first linked 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) to early menopause while studying women who were exposed to it after a chemical plant exploded in 1976 near Seveso, Italy. A 2005 study of 616 women from Seveso estimated that 10-fold elevations in serum TCDD were associated with a 6% nonsignificant increase in risk of early menopause.<sup>6</sup> The mean age of natural menopause among the exposed women was 49.2 years, which the authors noted was lower than the mean age of 50.9 years reported by a different study of more than 4,300 nonexposed Italian women conducted during the same time period.<sup>25</sup>

Citing animal studies, the authors of the 2005 study suggested that TCDD might lower the age of menopause by compromising the hypothalamic-pituitary axis, making women less sensitive to estrogen while also decreasing ovarian weights and follicle numbers.

Ten years later, the University of Colorado's Grindler led a team that analyzed data gathered by the National Health and



The environmental exposure associated most consistently with earlier menopausal age is smoking. This link first became evident during the 1970s, when research began linking early menopause with exposure to tobacco smoke. Recently, investigators discovered that secondhand smoke exposure may also accelerate the time to menopause. © iordani/Shutterstock.

Nutrition Examination Survey (NHANES) from 1999 to 2008.<sup>3</sup> Administered by the Centers for Disease Control and Prevention, NHANES collects health and demographic data, reproductive information, and serum and urine samples from representative groups within the general U.S. population.

Grindler and her colleagues analyzed 111 chemicals that were known reproductive toxicants or had half-lives in the body of more than one year. They then focused on 15 chemicals that, according to their analysis of NHANES data, were positively associated with younger menopausal age. Nine of the chemicals were PCBs, three were pesticides [including beta-hexachloro-cyclohexane, mirex, and dichlorodiphenyldichloroethylene (DDE), a metabolite of dichlorodiphenyltrichloroethylene (DDT)], one was in the dioxin/furan category, and the other two were phthalates.

Among the most-exposed women, average differences in age at menopause ranged from 1.77 years younger for 1,2,3,4,6,7,8-heptachlorodibenzofuran (the smallest statistically significant difference) to 3.8 years younger for mono-(2-ethyl-5-hydroxy-hexyl)phthalate, compared with less-exposed women. The authors speculated that chemicals such as these might contribute to early menopause either by slowly damaging the follicular pool, resulting in primary ovarian insufficiency, or by impeding the production of oocytes *in utero*, although non-causal mechanisms are also possible. The authors reported a mean age at menopause of 45.5 years among women evaluated in the study.

Recently, a team of investigators studied a proposed link between early menopause and elevated serum levels of perfluorooctanoic acid (PFOA), an industrial chemical used in several nonstick and stain-repellant applications.<sup>26</sup> Manufactured for decades, PFOA is now widespread in the biosphere, and most people have some in their bodies.<sup>27</sup> The chemical accumulates in blood, so women of reproductive age will eliminate some of it when they menstruate.

This association was reported in two prior studies of polyfluoroalkyl chemicals (PFCs) including PFOA. One assessed background exposure levels measured by NHANES, and the other involved a community in the Mid-Ohio Valley that was exposed to PFC-polluted groundwater for decades.<sup>28,29</sup> Both studies determined whether women were postmenopausal at the same time their PFCs were measured.



Another environmental exposure linked to early menopause was observed in women who were exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) after a chemical plant exploded in 1976 near Seveso, Italy. The study included women who would have been at least 15 years old at the time of the disaster. The authors hypothesized that TCDD might lower the age of menopause by compromising the hypothalamic-pituitary axis, making women less sensitive to estrogen while also decreasing ovarian weights and follicle numbers. © Mondadori Portfolio/Getty Images.

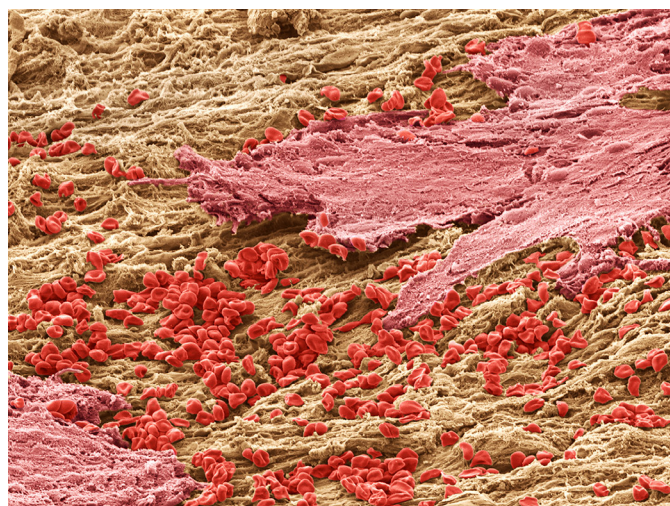
The first study found that women who had undergone menopause earlier had higher serum levels of PFCs than those who started menopause later.<sup>29</sup> The other showed that women with PFC concentrations in the four highest quintiles were more likely to have undergone menopause than women in the same age group with the lowest levels.<sup>30</sup> The authors of these studies suggested that higher exposures to PFCs may have caused women to enter menopause sooner, although they noted that the findings may be due to reverse causation.

For the new analysis of the Mid-Ohio Valley cohort, Radhika Dhingra, who is currently a research scientist at the U.S. Environmental Protection Agency, developed a longitudinal model using estimates of individuals' PFOA blood concentrations for each year from 1951 onward.<sup>27</sup> This model enabled her to assess the direction of the temporal relationship between PFC exposures and menopause—in other words, whether a woman's levels of PFCs affected her age at menopause or vice versa. Dhingra suspected that the association between early menopause and higher PFOA levels reported in the earlier studies simply reflected accumulating levels of the chemical in older women who were no longer losing blood through menstruation. And her modeled results supported that suspicion. "We could not detect a signal," she says. "If suggestive for that signal at all, the results were incredibly weak."

## A Search for Mechanisms

Jodi Flaws, a professor in the College of Veterinary Medicine at the University of Illinois at Urbana-Champaign, says that a fuller accounting of potential mechanisms linking EDCs with early menopause is elusive. "The pituitary and ovary interact through feedback loops, so when we see an outcome on the ovary, it is hard to know if it is because the chemical targeted the ovary or whether the chemical altered FSH/LH levels from the pituitary, which in turn altered the ovary," she says. "We simply do not have enough data from whole animal or human studies to know for sure."

Hoping to address gaps in the mechanistic data, Siobán Harlow, a professor of epidemiology at the University of Michigan, is codirecting a new longitudinal study of EDC



Studies of women with high body burdens of PFOA suggested that the chemical may have been responsible for early menopause in these populations. A later study concluded that the appearance of causality between higher PFOA levels and early menopause simply reflected the fact that postmenopausal women had begun accumulating PFOA while premenopausal women continued releasing the chemical in their menstrual blood. © Steve Gschmeissner/Science Source.

exposure in the SWAN cohort. Study staff collected blood and urine samples as enrolled women progressed from their reproductive years through menopause and analyzed them for biological markers, such as levels of estradiol (the most potent form of estrogen), FSH, and anti-Müllerian hormone, which reflects follicular counts in the ovaries. They also collected information on the women's cardiovascular function, lipids, blood glucose, bone mineral density, cognitive functioning, and mental health.

Now SWAN investigators will analyze the archived samples for 80 heavy metals and EDCs; they will study their possible effects on the timing of reproductive aging as well as on the expression levels of various hormones and how they interact during key phases of the menopausal transition. "Some studies suggest EDCs can lower FSH so that it is not able to ramp up follicular development and functionality, and that could result in an earlier age at menopause," Harlow says. "That's the sort of mechanism we'll be able to look at in detail—what we're really interested in is how these chemicals alter the internal endocrine environment."

Ideally, animal studies could provide further mechanistic insights, but most laboratory species do not share fundamental features of the human reproductive cycle. For instance, where humans have a roughly 28-day menstrual cycle, rodents have an estrous cycle that lasts just 4–5 days, and they do not menstruate.<sup>30</sup> Moreover, although it is possible to surgically remove a rodent's ovaries to simulate menopause, to date, there has been no way to simulate perimenopause.

To address that shortcoming, the University of Arizona's Hoyer codeveloped a rodent model of perimenopause that relies on an industrial chemical called 4-vinylcyclohexene diepoxide, which selectively kills ovarian follicles of mice and rats without affecting other tissues.<sup>31</sup> Hoyer explains that after 15 consecutive days of dosing, the animals cycle through estrus for approximately 2 months until their follicles are depleted. Fewer dosing days will prolong the time to ovarian failure, "and meanwhile, the animal's estrogen levels become progressively erratic," Hoyer says. "So you are left with a younger animal that's going through something that looks a lot like perimenopause." Hoyer proposes that after chemically inducing perimenopause, investigators could dose the animals with EDCs and then determine if the exposures accelerate ovarian failure, just as they might accelerate menopause in exposed women.

These ongoing research efforts will shed new light on the subtle ways that chemicals accelerate a fundamental transformation in a woman's life. Moreover, they comprise a new focus on aging that is long overdue in environmental health research and chemical risk assessment, according to Linda Birnbaum, director of the National Institute of Environmental Health Sciences.

Birnbaum says that apart from hastening menopause, some chemicals might harm older women disproportionately with age comes a diminished reserve capacity to fend off toxic effects. She recently coauthored a paper showing that postmenopausal women face greater risks of thyroid disease from exposure to polybrominated diphenyl ethers (e.g., industrial flame retardants) than younger women.<sup>32</sup> "Menopause and aging are important and frequently overlooked end points for us to consider," Birnbaum says. "This is all a fertile area for scientific investigation."

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